ISSN: 0974 – 3987
IJBST (2018), 11(7):60-65
DOI: http://doi.org/10.5281/zenodo.1493684

Stem Cell Immunotherapy for HIV Patients and Drawbacks

Imesha Rashmini Rathnayaka[1], Nivethika Sivakumaran[2]

1 & 2 Department of Biomedical Science, International College of Business and Technology, No 36, De Kretser Place, Bambalapitiya, Colombo 04, SRI LANKA
2 School of Science, Edulink International Campus, No 6, Glen Aber Place, Bambalapitiya, Colombo 04, SRI LANKA
snivethika25@gmail.com, imasharashmini@gmail.com

ABSTRACT:
Stem cell transplantation immunotherapy for HIV emerges since the 1980s. This therapy is can be used to reestablish the immune system of HIV patients. The ultimate goal of stem cell transplantation is clearing the virus from the patient's body. Dominating strategies in this field are combination of gene editing mechanisms with stem cell therapy to develop cytotoxic anti-HIV cells, modify stem cells using artificial and natural stem cell sources etc. Stem cell transplantation with modified zinc finger nuclease might be a promising cure for HIV infection in the future.

Key words: Cytotoxic, HIV, Immunotherapy, Lentivirus

INTRODUCTION

HIV (Human Immunodeficiency Virus) is retrovirus in the family of lentivirus. Once it reverses transcribe and integrate into to the human DNA it can be characterized as HIV infection. HIV is M-tropic at an early stage and it infects tissue macrophages, microglia cells, dendritic cells etc. Later these viruses become T-tropic and infect CD4+ cells. These viruses also need a co stimulator such as CCR5 and CXCR4 respectively. HIV is characterized as AIDS when the CD4+ count is less than 200 cells/mm3. AIDS patients are vulnerable to many opportunistic pathogens, and death occurs due to immune incompetence.

Antiretroviral therapy (ART) is used to treat for the natural course of HIV infection. This therapy can efficiently control the entry of HIV virus, reverse transcription, integration, assembly, and release of virus from effector cells. But this therapy doesn't control the HIV DNA expression, which utilizes host mechanisms. CD4 T-cells are target cells for HIV infection. Hence HIV effect both cellular and humoral pathways of the immune system [1].

Stem Cell Therapies (SCT) can be used to enhance the CD4+ count. Therefore these methods play a vital role in modern HIV immunotherapy. Any viable stem transplantation can either be categorized as Isogonic (between identical twins), autogenic (within the same individual) and allogeneic (within same species). Xenogenic (within different species) transplantation is not very much practiced due to ethical reasons.

HISTORY OF STEM CELL IMMUNOTHERAPY FOR HIV PATIENTS

Stem cell immunotherapy for HIV was first started in 1984 which was a Syngeneic Stem

ISSN: 0974 – 3987
IJBST (2018), 11(7):60-65
DOI: http://doi.org/10.5281/zenodo.1493684

Cell Transplantation. This was followed by an allogeneic. Allogeneic stem cell transplantation was started in 1989. Together with the advancement of genetic engineering first genetically modified allogeneic stem cell transplantation was done in 2001 [2, 3].

Cord Blood has pluripotent stem cells. Hence these cells have the potential to differentiate into any type of cells. First transplantation with cord blood stem cells was done in 2005. Once scientist identified the CCR5-delt 32 homozygous mutation, first cord blood transplantation with CCR5-delta 32 was done in 2013. In the last year, 2017 hematopoietic stem cells were genetically repaired to detect HIV infected cells inpatient and to destroy them by the transplanted cell [4, 5, 6].

INTERACTIONS DURING STEM CELL TRANSPLANTATION IN HIV PATIENTS

Some ethnicities are resistant to HIV due to their genetic mutations, this is known as CCR5-delta 32 mutation. As the name indicates this effect the CCR5 co-stimulatory protein. Ethnic groups who have homozygous for this specific mutation are resistant to HIV. This was clinically tested in Berlin 2007. A patient suffered from both leukaemia and HIV. Researchers replaced his bone marrow with a bone marrow bares CCR5 – delta 32 mutation. This treatment was focused on leukaemia. But as side effect patient also became resistant to HIV [7].

Cyclosporine A is used as an immunosuppressive agent in HIV infection. Hence it decreases the T cell activation by deletion of signalling pathways to T cells. Therefore the spreading of infection may be altered. But several studies also reveal that this depletion of T cell activation in may lead to long-term beneficial effects. Allogeneic stem cell transplants use Anti thymocyte antibodies (ATG) as an immunosuppressive therapy. These Antibodies leads to a chronic reduction of CD4+ cells in HIV patients. Hence these antibodies affect both infected and non-infected T cell within the patient.
But this will limit only for the period of usage. However, according to several retrospective studies, it proves that HIV+ patients indicated a slightly lower survival rate after stem cell therapies compared to stem cell transplants for other diseased patients [8].

GENETICALLY MODIFIED HSC (HEMATOPOIETIC STEM CELLS)-BASED IMMUNOTHERAPY

The use of a HSC-based therapeutic approach leads to different lineages of blood cell development. This method also can used to enhance the immune response towards HIV. Hence these cells will lead to developing HIV target cells that have normal cellular differentiation pathways. Therefore activation and expansion of antigen-reactive cells in the periphery lead to the differentiation of these cells into long-term memory cells through natural mechanisms. Also, hematopoietic stem cell-based approach would lead to generation of long-term naïve HIV-targeted cells. These modified cells thus lack the issues of developmental biasing, exhaustion, functional impairment that may sometimes occur with other ex-vivo methods. But the development of these stem cell-based techniques is challenged due to the paucity of experimental systems that paves the close examination of human hematopoietic events

ISSN: 0974 – 3987
IJBST (2018), 11(7):60-65
DOI: http://doi.org/10.5281/zenodo.1493684

and cellular function. Recent advances have been made in the development of HSC-based programming as a viable therapeutic strategy. A major target of stem cell-based immune therapeutic strategies is the development of B cells that produce neutralizing antibodies or cytotoxic T cells that target and kill infected cells. Several studies have proved the ability to program B cells such that human HSCs to express an anti-HIV neutralizing antibody following differentiation in vitro and in vivo [9].

These studies suggest that principles can be further explored to utilize multiple antibodies against HIV. Genetically modified B cell responses may be useful to uplift cellular immune responses specifically in the innate and mucosal immune compartments. Development in this method may lead to the development of other chimeric receptors that will target the cellular immunity. Due to the vital role of T cells throughout the HIV infection, engineering of HSCs stimulates antiviral T cell immunity is another fascinating strategy for investigation as a therapeutic approach. Previous studies with human cells demonstrated that ability of human HSCs to develop into T cells with differentiation on murine Delta-like 1 molecule-express in stromal cell lines. This process of development and thymic positive and negative selection from HSC progenitors literally minimize the possibility of producing autoreactive cells. Also stem cell-based methods lead to a longer engraftment of functionally capable gene-marked cells on par with peripheral cell-based modification. Due to the technological advancement, it is possible to develop molecularly cloned T cell receptors to have many viral antigens in different HLA (Human Leukocyte Antigen) types. But this is would not be necessary to achieve the high levels of genetic transduction in order to protect progeny of cells from infection or gene therapy models [10].

PRE-TRANSPLANT CONDITIONING REGIMENS

Although the animal studies described above clearly demonstrate the feasibility and efficacy of transplanting HIV-resistant HSCs, a major question remains: that is about how one can achieve similar engraftment in people infected with HIV. From large scale animal studies, we can understand that HSC engraftment without conditioning is likely to be very low, especially given the limited cell numbers available for humans or large animals. Different conditioning approaches are studied in nonhuman primate models. These allow understanding and analysing the level of engraftment that is needed to provide protection and to be effective. Today high-dose irradiation regimens are commonly used for transplantation or stem cell gene therapy studies [11,12].

Other advantages of nonhuman primate studies include the ability to comprehensively analyze latent virus reservoirs by analyzing peripheral blood products. In the next several years, we hope that effective and reasonably safe conditioning regimens will be developed using nonhuman primate models. Since HSCs can be expanded ex vivo, alternative and better-tolerated conditioning regimens could be considered or conditioning regimens might be totally avoided. A good alternative

ISSN: 0974 – 3987
IJBST (2018), 11(7):60-65
DOI: http://doi.org/10.5281/zenodo.1493684

strategy to optimize engraftment has been proposed. That is, to inject myeloerythroid cells directly into the bone marrow instead of intravenously. Several investigators have suggested this differential engraftment pattern. Probably soon it will be possible modify stem cells ex vivo, for transplantation without harmful conditions into healthy individuals on effective antiretroviral therapy. Even though gene modification of stem cells is an expensive intervention for HIV, it is still cost-effective than the cost of decades on antiretroviral therapy [13].

APPROACHES FOR GENETICALLY MODIFICATION OF HSCS AGAINST HIV

There are two main approaches for modifying HSCs. They are as follows, disruption of cellular genes involved in HIV entry , CCR5 is a G protein-coupled chemokine receptor that functions also as a critical coreceptor for the entry of "R5" strains of HIV. But CCR5 is not critical for normal immune function. Since CCR5-D32 (D32) mutation is present in they are less susceptible to HIV. Hence it's a good antiviral target [14]. The effectiveness of permanent elimination of CCR5 was illustrated in only cured HIV patients, also known as the "Berlin patient".

Another gene that interfere with HIV infection therapeutics is gp41-derived peptide (C46), which is structurally similar to the FDA-approved fusion inhibitor enfuvirtide. It can effectively inhibit HIV entry. This therapy has been proven to be well tolerated. The addition of C46 into HSCs was also evaluated in a macaque model of HIV infection modified cells were protected from subsequent HIV challenge as well. Also, this resistance seems to be high and rapid when it is used in the absence of a fully suppressive antiretroviral. But the barrier for developing C46 resistance may sometimes be greater than for enfuvirtide resistance. Hence this remedy needs in vivo experimental evaluation [12].

DRAWBACKS

Berkhout and his colleagues prove that high mutation rate in HIV virus may occur despite the gene therapy used. Mathematical models used in linear models of infection gene therapy suggest that cells that are used for gene therapy should have a longer lifespan and higher proliferation rate to compensate for the HIV infection more effectively. Hence modified stem cells with these capabilities may have a higher rate of proliferation than peripheral stem cells [13, 14]

Stem cell transplantation is very risky. Dr. Kristina Allers, a doctor at the Charite University Medicine in Berlin state that about one-third (that is almost thirty percent) of patients that are subjected bone marrow transplant procedure die. These patients have a very low chance of getting a graft that will not reject by the host. Patients that suffer from HIV and several other cancers have a very low chance of success [7].

CONCLUSION

Stem cell transplant for HIV patients is a navel field. But still, mechanisms of rejection of stem cell transplants by host own cells are poorly understood. Stem cell transplantation is not yet considered as a standard treatment method for HIV patients. At the present cell-

ISSN: 0974 – 3987
IJBST (2018), 11(7):60-65
DOI: http://doi.org/10.5281/zenodo.1493684

based immunotherapy with stem cells is an emerging field.

Since CCR5-delta32 mutation is proven to be resistance towards HIV, researchers try to program patients to own cells to have this mutation. This is by taking stem cells from patient's blood and reacting them with zinc finger nuclease. Even though this has not experimented in humans, if this method further develops chances of rejection will be minimized. Researchers also believe that these cells will have a high lifespan and a high proliferative rate [7].

These strategies will develop within upcoming years, and therapeutic applications towards an exact cure for HIV using stem cell therapy will be developed. Hence the future generation would able step to a world, without fear of HIV infection.

ACKNOWLEDGEMENTS

Special gratitude I give to all well-wishers for the support and encouragement.

REFERENCES

[1] Gene therapy using CAR T-cells could provide long-term protection against HIV -- ScienceDaily. (2017). Retrieved April 8, 2018, from https://www.sciencedaily.com/releases/2017/12/171228145216.htm

[2] Group, N. publishing. (2005). Unrelated cord blood transplantation for a human immunodeficiency virus-1-seropositive patient with acute lymphoblastic leukemia. Nature, 36, 261–262. https://doi.org/10.1038/sj.bmt.1705028

[3] Hill, A. L., Rosenbloom, D. I. S., Fu, F., Nowak, M. A., & Siliciano, R. F. (2014). Predicting the outcomes of treatment to eradicate the latent reservoir for HIV-1,111(37),2–7. https://doi.org/10.1073/pnas.1406663111

[4] Hütter, G. (2016). Stem cell transplantation in strategies for curing HIV / AIDS. AIDS Research and Therapy, 13(31), 1–8. https://doi.org/10.1186/s12981-016-0114-y

[5] appas, S. (2011). Risky Treatment May Be Answer for Small Group of HIV Patients. Retrieved April 8, 2018, from https://www.livescience.com/13098-hiv-treatment-stem-cells-aids.html

[6] Sivakumaran, N., Rathnayaka, I. R., Shabbir, R., & Wimalsinghe, S. S. (2018). Umbilical Cord Blood Banking and its Therapeutic Uses. International Journal of Scientific Research and Innovative Technology, 5(1), 160–172.

[7] Verdonck, L., Gast, G. de, Lange, J., Schuurman, H., Dekker, A., & Bast, B. (1988). Syngeneic leukocytes together with Suramin failed to improve immunodeficiency in a case of. Blood, 71(3), 666–671.

[8] Westerhout, E. M., Ooms, M., Vink, M., Das, A. T., & Berkhout, B. (2005). HIV-1 can escape from RNA interference by evolving an alternative structure in its RNA genome. Nucleic Acids Research, 33(2), 796–804. https://doi.org/10.1093/nar/gki220

[9] Joseph A, Zheng JH, Chen K, Dutta M, Chen C, Stiegler G, et al. Inhibition of In Vivo HIV Infection in Humanized Mice by Gene Therapy of Human Hematopoietic Stem Cells with a Lentiviral Vector Encoding a Broadly Neutralizing Anti-HIV Antibody □. J Virol 2010;84:6645–53. doi:10.1128/JVI.02339-09.

[10] Wiesel M, Walton ÃS, Ã ÃKR, Oxenius A, Cells CDT. Virus-specific CD8 T cells : activation , differentiation and memory formation. APMIS 2009:356–81.doi:10.1111/j.1600-0463.2009.02459.x.

[11] Horn PA, Topp MS, Morris JC, Riddell SR, Kiem H. Highly efficient gene transfer into baboon marrow repopulating cells using

ISSN: 0974 – 3987
IJBST (2018), 11(7):60-65
DOI: http://doi.org/10.5281/zenodo.1493684

GALV-pseudotype oncoretroviral vectors produced by human packaging cells. Blood 2002;100:3960–7. doi:10.1182/blood-2002-05-1359.Supported.

[12] Beard BC, Trobridge GD, Ironside C, Mccune JS, Adair JE, Kiem H. Efficient and stable MGMT-mediated selection of long-term repopulating stem cells in nonhuman primates. J Clin Invest 2010;120. doi:10.1172/JCI40767DS1.

[13] Zaia†, G. H. and J. A. (2011). Allogeneic haematopoietic stem cell transplantation in patients with human immunodeficiency virus : the experiences of more than 25 years. The Journal of Translational Immunology, 163,284–295.https://doi.org/10.1111/j.1365-2249.2010.04312.x

[14] Zhang, J., & Crumpacker, C. (2013). Eradication of HIV and cure of AIDS , now and how ? Frontiers in Immunology,4(October),1–9. https://doi.org/10.3389/fimmu.2013.00337Hammersley, M., &Traianou, A. (2012). Ethics and Educational Research. *British Educational Research Association, 1*